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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,898	10/26/2006	Ellen Jessouroun	NIH275.001NP2	9576

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EXAMINER	
ARCHIE, NINA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,898	JESSOUROUN ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed on 6-1-2009. Claims 1-20 are pending and under examination. Claims 1, 9, 15, and 17 are amended.

Rejections Withdrawn

2. In view of the Applicant's amendment and remark following rejections are withdrawn.

a) The rejection of claims 1-20 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending US Application 10,566,889 is withdrawn from consideration due to the instant application's and copending application's amendments to the claims thereto, and also to applicants cancellation of claims 9-12 of copending application.

Claims

3. The following claims 1-20 apply to the rejections below.

The claims are drawn to a method for preparing a conjugate vaccine in commercial volumes, the method comprising: reacting a polysaccharide with an oxidizing agent, whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine dichloride at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained; purifying said solution of hydrazine-activated protein under conditions standardized to process at least five liters of solution; reacting the aldehyde-activated polysaccharide with the hydrazine-activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with adipic acid dihydrazide; and purifying the resulting solution under conditions standardized to process a volume of at least two liters, whereby a conjugate vaccine capable of stimulating an immune response is obtained in commercial volumes (claim 1), wherein the oxidizing agent comprises NaIO4 (claim 2), wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged with a HEPES buffer (claim 3), wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged to a pH of from about 7 to about 8 (claim 4), wherein the solution of the hydrazine-activated protein is buffer exchanged with a Na2CO3 buffer (claim 5), wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0 (claim 6), wherein a pH of the solution of the hydrazine-activated

protein is raised to from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0 (claim 7), wherein the aldehyde-activated polysaccharide is reacted with the hydrazine-activated protein at a ratio of from about 1:1.6 to about 1:5 (claim 8), wherein said purifying the resulting solution comprises further comprising the step of diafiltrating the conjugate vaccine, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine (claim 9), further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration, yielding a concentrated purified conjugate vaccine (claim 10), further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine, yielding a stabilized conjugate vaccine (claim 11), further comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine (claim 12), wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus polysaccharides, *Hemophilus influenzae type b* polysaccharide, Vi polysaccharide of *Salmonnella typhi*, and *Group B Streptococcus* polysaccharides (claim 13), wherein the protein is selected from the group consisting of tetanus toxoid, diptheria toxoid, CRM197, and meningococcal protein (claim 14); a method for preparing a conjugate vaccine in commercial volumes, the method comprising: reacting a polysaccharide with an oxidizing agent, whereby a solution of an aldehyde-activated polysaccharide is obtained; buffer exchanging the solution of the aldehyde-activated polysaccharide to a pH of from about 7 to about 8; reacting a protein with hydrazine dichloride at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained; raising a pH of the solution of the hydrazine-activated protein to from about 7.0 to about 11 and thereafter buffer exchanging the solution of the hydrazine-activated protein to a pH of from about 10.0 to about 11.0 purifying said solution of hydrazine-activated protein under conditions standardized to process at least five liters of solution; reacting the aldehyde-activated polysaccharide with the hydrazine-activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with adipic acid dihydrazide, and purifying the resulting solution under conditions standardized to process a volume of at least two liters, whereby a conjugate vaccine capable of stimulating an immune response is obtained in commercial volumes (claim 15), wherein the aldehyde-activated

polysaccharide is reacted with the hydrazine-activated protein at a ratio of from about 1:1.6 to about 1:5 (claim 16), wherein said purifying the resulting solution comprises further comprising the step of diafiltrating the conjugate vaccine, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine (claim 17), further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration, yielding a concentrated purified conjugate vaccine (claim 18), further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine, yielding a stabilized conjugate vaccine (claim 19), wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus polysaccharides, *Hemophilus influenzae type b* polysaccharide, Vi polysaccharide of *Salmonnella typhi*, and *Group B Streptococcus* polysaccharides, and wherein the protein is selected from the group of consisting of tetanus toxoid, diptheria toxoid, CRM_{197}, and meningococcal protein (claim 20).

New Grounds of Rejection

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to independent claim 1 and 15, and dependent claims 4, 6-8, and 16 the recitation “of from about” is relative which renders the claim indefinite. The recitation “of from about” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

As to dependent claims 9 and 17, the claims are rendered vague and indefinite by the use of the term “substantially”. The term "substantially" is a relative term that is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections-35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz US Patent No. 6,800,728 Date October 5, 2004 US Filing Date March 22, 2001, Ryall et al US Patent No. 5,965,714 Date October 12, 1999, Kuriyama et al US Patent No. 4,963,232 Date October 16, 1990, as evidenced by Behr et al 2003 Tetrahedron 59 pgs. 543-553.

Schwartz teaches a method of immobilizing a biological molecule, comprising: preparing a conjugate bound to a biological molecule, wherein the conjugate is formed from a carrier protein, wherein the biomolecule is a bacterial polysaccharide (see claims and column 3 lines 55-65). Schwartz teaches incorporating a carbonyl group on a biomolecule to produce dialdehydes by periodate-mediated oxidation (see column 22 lines 30-45). Schwartz further teach a bacterial polysaccharide, oxidized with sodium periodate to form dialdehyde moieties (see Example 29 column 34, column 29 lines 1-40 and column 30 lines 1-20), which correlates to a method for preparing a conjugate, whereby a solution of an aldehyde-activated polysaccharide is obtained. Schwartz teach said conjugate can be prepared by the addition of a reagent in a solution comprising a biomolecule such as sodium periodate in a non-nucleophilic buffer at pH 7.0-8.0 (see column 24 lines 45-50), which correlates to a method, wherein the solution of the aldehyde-activated polysaccharide is a buffer exchanged with a HEPES buffer as evidenced by Behr et al (see pg. 546 first paragraph). Schwartz teaches modifying protein carriers such as tetanus toxoid

or diphtheria toxoid (column 20 lines 1-5), binding a protein with a hydrazine in a buffer solution at a pH of 4.7 (see Figure 1, 4. Bifunctional Carbonyl Reagents Section, Example 11), which correlates to method comprising the binding of a protein with hydrazine at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained. Schwartz teaches a method of forming crosslinks between protein-polymer conjugates (column 24 lines 50-65 and (column 25 lines 1-10) in the presence of sodium cyanoborohydride (see column 24 lines 60-67)) between a range of 4.7 and 7.4 (see column 25 lines 30-45). Schwartz teach applying a conjugate comprising a hydrazine modified carrier to react to the dialdehyde moieties of a bacterial polysaccharide that have been oxidized forming a hydrazone bond (see claims and Example 29). Schwartz teaches a aldehyde-activated polysaccharide with concentration of 5 mg/ml (see Example 29) and hydrazine-activated protein polysaccharide with concentration 5mg/ml (Example 11) at a ratio of 1:1. Schwartz teaches a method of preparing conjugates for in vivo uses as vaccines, thus the method of Schwartz would necessarily teach a conjugate vaccines in commercial volumes, wherein a conjugate vaccine is capable of stimulating an immune response obtained in commercial volumes as evidenced to the contrary.

Schwartz does not teach a method for preparing a conjugate comprising method steps, reacting a protein specifically with hydrazine dichloride in a solution, purifying the solution of hydrazine-activated protein under conditions standardized to process at least five liters of solution, neutralizing unreacted aldehyde groups with adipic acid dihydrazide; and purifying the resulting solution under conditions standardized to process a volume of at least two liters, wherein said purifying the resulting solution comprises further comprising the step of diafiltrating the conjugate vaccine, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine, further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration, yielding a concentrated purified conjugate vaccine, further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine, yielding a stabilized conjugate vaccine, further comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine, wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus

polysaccharides, *Hemophilus influenzae type b* polysaccharide, Vi polysaccharide of *Salmonnella typhi*, and *Group B Streptococcus* polysaccharides.

Ryall et al teach a method for preparing a construct comprising a bacterial polysaccharide comprising Streptococcus pneumoniae covalently attached to a protein molecule (see claims and column 15 lines 20-25), comprising mixing unreduced depolymerized polysaccharide chains with adipic dihydrazide (see column 7 lines 30-35), which correlates to neutralizing unreacted aldehyde groups with adipic acid dihydrazide and purifying the resulting solution under conditions standardized to process a volume of at least two liters. Ryall et al teach a method step of diafiltering a conjugate (see column 19 lines 30-50), whereby substantially all unreacted compounds and unconjugated polysaccharides are removed yielding a purified conjugate vaccine. Ryall et al teach a method further comprising depolymerized polysaccharide purified by ultrafiltration and a protein molecule which can be purified by ultrafiltration using a FILTRON-type minisette tangential flow filtration unit equipped with a 1,000 molecular weight cutoff (MWCO) Omega modified polyethersulfone screen channel unit cassette (see column 19 lines 40-50), which correlate to a method of yielding a concentrated purified conjugate vaccine, a method comprising purifying the resulting solution under conditions standardized to process at least five liters of solution. Ryall et al teach compositions comprising the construct may be in admixture with a suitable carrier glucose or the like, which correlate to a method further comprising the step of adding saccharose as a stabilizer to the concentrated purified vaccine yielding a stabilized conjugate vaccine.

Kuriyama et al teach hydrazinium monochloride, also known as hydrazine dichloride (as evidenced by Material Safety Data Sheet from Fischer Scientific (see attachment)). Moreover Kuriyama et al teach hydrazinium monochloride are preferably usable in a concentration-distillation process comprising distilling an aqueous solution of a product in the presence of hydrazinium monochloride to concentrate the aqueous solution of a product by distilling water and the majority of the total organic carbon constituents off and further separating the resultant concentrate as a bottom product, to further comprise distilling the resultant concentrate to recover a purified aqueous solution as a top product and separating an aqueous solution of the above salt as a bottom product in a solution (see column 3 lines 1-35 column 6 lines 1-8).

Schwartz teaches a method of using hydrazine to activate a protein so it can react with an aldehyde-activated polysaccharide which has carbon constituents. Furthermore, Kuriyama et al teach hydrazine dichloride is used in a concentration-distillation process to remove the majority of total organic carbon constituents to recover a purified product in a solution. Therefore the use of hydrazine dichloride in a concentration-distillation process constitutes an obvious variant of the method disclosed by Schwartz. Moreover since the use of hydrazine dichloride is known in the art with predictable results it is obvious to use it in the method of Schwartz. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

Schwartz and Ryan et al both teach methods for preparing a conjugate vaccines using bacterial polysaccharide. Furthermore, Ryan et al teach *Streptococcus pneumoniae* is used as a bacterial polysaccharide in a method for preparing a conjugate vaccine. Moreover, Ryan et al teach method steps comprising neutralizing unreacted aldehyde groups with adipic acid dihydrazide and purifying the resulting solution, diafiltering a conjugate, and concentrating the purified conjugate vaccine by tangential flow ultrafiltration, further comprising the step of adding saccharose as a stabilizer in a method for preparing a conjugate vaccine. Therefore the use of *Streptococcus pneumoniae* constitutes an obvious variant of the method disclosed by Schwartz. Moreover since the use of *Streptococcus pneumoniae* is known in the art with predictable results it is obvious to use it in the method of Schwartz. Also the use of the method steps of Ryan et al are well known in the art with predictable results, thus it remains obvious to combine the teachings of Schwartz and Ryan et al, even without an express statement of motivation. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

6. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz US Patent No. 6,800,728 Date October 5, 2004 US Filing Date March 22, 2001, Ryall et al US Patent No. 5,965,714 Date October 12, 1999, Kuriyama et al US Patent No. 4,963,232 Date October 16, 1990, and Donovan et al US Patent No. 5,480,643 Date January 2, 1996, Powell US Patent No. 5,066408 Date November 19, 1991, as evidenced by Behr et al 2003 Tetrahedron 59 pgs. 543-553.

Schwartz teaches a method of immobilizing a biological molecule, comprising: preparing a conjugate bound to a biological molecule, wherein the conjugate is formed from a carrier protein, wherein the biomolecule is a bacterial polysaccharide (see claims and column 3 lines 55-65). Schwartz teaches incorporating a carbonyl group on a biomolecule to produce dialdehydes by periodate-mediated oxidation (see column 22 lines 30-45). Schwartz further teach a bacterial polysaccharide, oxidized with sodium periodate to form dialdehyde moieties (see Example 29 column 34, column 29 lines 1-40 and column 30 lines 1-20), which correlates to a method for preparing a conjugate, whereby a solution of an aldehyde-activated polysaccharide is obtained. Schwartz teach said conjugate can be prepared by the addition of a reagent in a solution comprising a biomolecule such as sodium periodate in a non-nucleophilic buffer at pH 7.0-8.0 (see column 24 lines 45-50), which correlates to a method, wherein the solution of the aldehyde-activated polysaccharide is a buffer exchanged with a HEPES buffer as evidenced by Behr et al (see pg. 546 first paragraph). Schwartz teaches modifying protein carriers such as tetanus toxoid or diphtheria toxoid (column 20 lines 1-5), binding a protein with a hydrazine in a buffer solution at a pH of 4.7 (see Figure 1, 4. Bifunctional Carbonyl Reagents Section, Example 11), which correlates to method comprising the binding of a protein with hydrazine at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained. Schwartz teaches a method of forming crosslinks between protein-polymer conjugates (column 24 lines 50-65 and (column 25 lines 1-10) in the presence of sodium cyanoborohydride (see column 24 lines 60-67)) between a range of 4.7 and 7.4 (see column 25 lines 30-45). Schwartz teach applying a conjugate comprising a hydrazine modified carrier to react to the dialdehyde moieties of a bacterial polysaccharide that have been oxidized forming a hydrazone bond (see claims and Example 29). Schwartz teaches a aldehyde-activated polysaccharide with concentration of 5 mg/ml (see Example 29) and hydrazine-activated protein polysaccharide with concentration 5mg/ml (Example 11) at a ratio of

1:1. Schwartz teaches a method of preparing conjugates for in vivo uses as vaccines, thus the method of Schwartz would necessarily teach a conjugate vaccines in commercial volumes, wherein a conjugate vaccine is capable of stimulating an immune response obtained in commercial volumes as evidenced to the contrary.

Schwartz does not teach a method for preparing a conjugate comprising method steps, reacting a protein specifically with hydrazine dichloride in a solution, purifying the solution of hydrazine-activated protein under conditions standardized to process at least five liters of solution, neutralizing unreacted aldehyde groups with adipic acid dihydrazide; and purifying the resulting solution under conditions standardized to process a volume of at least two liters, wherein the solution of the hydrazine-activated protein is buffer exchanged with a Na2CO3 buffer, wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, wherein a pH of the solution of the hydrazine-activated protein is raised to from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, wherein said purifying the resulting solution comprises further comprising the step of diafiltrating the conjugate vaccine, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine, further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration, yielding a concentrated purified conjugate vaccine, further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine, yielding a stabilized conjugate vaccine, further comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine, wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus polysaccharides, *Hemophilus influenzae type b* polysaccharide, Vi polysaccharide of *Salmonnella typhi*, and *Group B Streptococcus* polysaccharides.

Ryall et al teach a method for preparing a construct comprising a bacterial polysaccharide comprising Streptococcus pneumoniae covalently attached to a protein molecule (see claims and column 15 lines 20-25), comprising mixing unreduced depolymerized polysaccharide chains with adipic dihydrazide (see column 7 lines 30-35), which correlates to neutralizing unreacted aldehyde groups with adipic acid dihydrazide and purifying the resulting solution under conditions standardized to process a volume of at least two liters. Ryall et al teach a method step

of diafiltering a conjugate (see column 19 lines 30-50), whereby substantially all unreacted compounds and unconjugated polysaccharides are removed yielding a purified conjugate vaccine. Ryall et al teach a method further comprising depolymerized polysaccharide purified by ultrafiltration and a protein molecule which can be purified by ultrafiltration using a FILTRON-type minisette tangential flow filtration unit equipped with a 1,000 molecular weight cutoff (MWCO) Omega modified polyethersulfone screen channel unit cassette (see column 19 lines 40-50), which correlate to a method of yielding a concentrated purified conjugate vaccine, a method comprising purifying the resulting solution under conditions standardized to process at least five liters of solution. Ryall et al teach compositions comprising the construct may be in admixture with a suitable carrier glucose or the like, which correlate to a method further comprising the step of adding saccharose as a stabilizer to the concentrated purified vaccine yielding a stabilized conjugate vaccine.

Kuriyama et al teach hydrazinium monochloride, also known as hydrazine dichloride (as evidenced by Material Safety Data Sheet from Fischer Scientific (see attachment)). Moreover Kuriyama et al teach hydrazinium monochloride are preferably usable in a concentration-distillation process comprising distilling an aqueous solution of a product in the presence of hydrazinium monochloride to concentrate the aqueous solution of a product by distilling water and the majority of the total organic carbon constituents off and further separating the resultant concentrate as a bottom product, to further comprise distilling the resultant concentrate to recover a purified aqueous solution as a top product and separating an aqueous solution of the above salt as a bottom product in a solution (see column 3 lines 1-35 column 6 lines 1-8).

Donovan et al teach a buffering agent to maintain a pH range for optimum activity when a dialdehyde composition is employed in an active form (see column 3 lines 20-28). Donovan et al teach a buffering agent such as sodium carbonate is preferable to add to maintain the pH at an optimum alkaline level for dialdehyde activity (see column 7 lines 59-67 column 8 lines 1-5).

Powell teach it is necessary to add an alkalyzer such as sodium carbonate (soda ash) to raise the pH to prevent the pH from dropping below 7.2 (see column 1 lines 65-69 and column 2 lines 1-10).

As to the limitations of dependent claims 6-7, a method wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10 to about 11.0 (claim 6),

wherein the hydrazine-activated protein is raised from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0 (claim 7). The references of Donovan et al and Powell et al do not specifically teach a buffer exchanged to a pH of from about 10 to about 11.0, wherein a pH solution is raised from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0 as claimed by the Applicants. The pH of a specific value is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955). Thus, optimization of general conditions is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal pH in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of pH would have been obvious at the time of applicant's invention.

Schwartz teaches a method of using hydrazine to activate a protein so it can react with aldehyde-activated polysaccharide which has carbon constituents. Furthermore, Kuriyama et al teach hydrazine dichloride is used in a concentration-distillation process to remove the majority of total organic carbon constituents to recover a purified product in a solution. Therefore the use of hydrazine dichloride in a concentration-distillation process constitutes an obvious variant of the method disclosed by Schwartz. Moreover since the use of hydrazine dichloride is known in the art with predictable results it is obvious to use it in the method of Schwartz. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

Schwartz and Ryan et al both teach methods for preparing a conjugate vaccines using bacterial polysaccharide. Furthermore, Ryan et al teach *Streptococcus pneumoniae* is used as a bacterial polysaccharide in a method for preparing a conjugate vaccine. Moreover, Ryan et al

teach method steps comprising neutralizing unreacted aldehyde groups with adipic acid dihydrazide and purifying the resulting solution, diafiltering a conjugate, and concentrating the purified conjugate vaccine by tangential flow ultrafiltration, further comprising the step of adding saccharose as a stabilizer in a method for preparing a conjugate vaccine. Therefore the use of *Streptococcus pneumoniae* constitutes an obvious variant of the method disclosed by Schwartz. Moreover since the use of *Streptococcus pneumoniae* is known in the art with predictable results it is obvious to use it in the method of Schwartz. Also the use of the method steps of Ryan et al are well known in the art with predictable results, thus it remains obvious to combine the teachings of Schwartz and Ryan et al, even without an express statement of motivation. KSR forcloses the argument that a specific teaching, suggestion, or motivation is required to support a finding a obviousness. See the recent Board Decision Ex parte Smith, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

It would have been prima facie obvious at the time the invention was made to use a buffer exchange with a sodium carbonate as taught by Donovan et al in the method as taught by Schwartz in order to take advantage of maintaining the pH of the hydrazine activated protein at an optimum alkaline level for dialdehyde activity.

One would have had reasonable expectation of success because sodium carbonate is used as a buffering agent (disclosed by Donovan et al) and has been shown to maintain a pH at an alkaline level, as being well known in the art.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina Archie
Examiner
Art Unit 1645

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645